



## General

### Guideline Title

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update.

### Bibliographic Source(s)

Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, Lee MT, Gage BF, Kimmel SE, Perera MA, Anderson JL, Pirmohamed M, Klein TE, Limdi NA, Cavallari LH, Wadelius M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. Clin Pharmacol Ther. 2017 Sep;102(3):397-404. [46 references] [PubMed](#)

### Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report [Clinical Practice Guidelines We Can Trust](#).

■■■■= Poor ■■■■= Fair ■■■■= Good ■■■■= Very Good ■■■■= Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
■■■■	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group

UNKNOWN	Methodologist Involvement
■□□□	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
■■■■■	Search Strategy
■■■■■	Study Selection
■■■■■	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
■■■■■	Grading the Quality or Strength of Evidence
■■■■■	Benefits and Harms of Recommendations
■■■■■	Evidence Summary Supporting Recommendations
■■■■■	Rating the Strength of Recommendations
■■■■■	Specific and Unambiguous Articulation of Recommendations
■■□□□	External Review
■■■■■	Updating

## Recommendations

### Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

#### Genetic Test Interpretation

##### Cytochrome P450 2C9 (*CYP2C9*)

Clinical laboratories typically report *CYP2C9* genotype results using the star (\*) allele nomenclature system and an interpretation that includes a predicted metabolizer phenotype (*CYP2C9* allele definition table [see the "Availability of Companion Documents" field]). Most U.S. Food and Drug Administration (FDA)-approved *CYP2C9* tests include only \*2 and \*3, which is not as informative for African ancestry populations; however, some clinical laboratories may offer expanded *CYP2C9* panels validated as laboratory developed tests (LDTs) (for allele frequencies, see *CYP2C9* frequency table [see the "Availability of Companion Documents" field]).

##### Vitamin K Epoxide Reductase Complex Subunit 1 (*VKORC1*)

Clinical laboratories typically report *VKORC1* genotype results by c.-1639G>A (or the linked 1173C>T; rs9934438) genotype (e.g., G/A) and an interpretation on warfarin sensitivity (*VKORC1* allele definition table [see the "Availability of Companion Documents" field]). Most commercial genotyping platforms do not detect rare *VKORC1* variants that have been associated with warfarin resistance (*VKORC1* frequency

table [see the "Availability of Companion Documents" field]).

#### Cytochrome P450 4F2 (*CYP4F2*)

Although not as commonly tested for as *CYP2C9* and *VKORC1*, some clinical laboratories may also test for *CYP4F2* using a targeted genotyping laboratory developed test to detect *CYP4F2*\*3 (c.1297G>A, p.Val433Met; rs2108622) variant (*CYP4F2* allele definition table [see the "Availability of Companion Documents" field]). Results are typically reported by nucleotide (e.g., G/A), amino acid (e.g., Val/Met) or star (\*) allele (\*1/\*3) genotype and an interpretation related to warfarin dosing.

#### *CYP2C* rs12777823

Given the recent identification of the association between rs12777823 (g.96405502G>A) and warfarin dosing among African Americans, most clinical laboratories do not currently include this non-coding variant in their warfarin pharmacogenetic genotyping panels. However, the increasing accessibility of clinical research genomics programs that return actionable results and the notable effect of this variant among African Americans suggests that some patients may have genotype results for this variant in the future. Results would likely be reported by genotype (e.g., G/A) and an interpretation related to warfarin dosing.

#### Genetic Test Options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry (<http://www.ncbi.nlm.nih.gov/gtr/> ).

#### Incidental Findings

No diseases have been linked to common *CYP2C9* variants independent of drug metabolism and response. Similarly, no diseases have been consistently linked to common *VKORC1* and *CYP4F2* variants that are interrogated in warfarin response tests. However, homozygosity for rare coding mutations in *VKORC1* are a known cause of combined deficiency of vitamin K-dependent clotting factors-2 (*VKCFD2*), which is a rare and potentially fatal bleeding disorder that can be reversed by oral administration of vitamin K.

#### Therapeutic Recommendations: Adults

##### Recommendations for Warfarin Maintenance (Chronic) Dosage Based on Genetic Information

The authors use the three-tiered rating system, described in the "Rating Scheme for the Strength of the Recommendations" field, in which ratings of strong, moderate, and optional are applied based on the evidence reviewed. The recommendations for dosing based on genotype contained herein include recommendations and are derived from numerous observational and prospective studies, and randomized trials that suggest the ability to more accurately identify stable therapeutic warfarin dose requirements through the use of both genetic and clinical information. Data from prospective studies and randomized controlled trials are equivocal on whether the improvement in dosing prediction by pharmacogenetics dosing leads to improved clinical outcomes. The majority of the literature underpinning these guidelines arises from individuals of European ancestry, African Americans, and East Asians. However, the more limited literature in other populations generally suggests the guidelines are appropriate in them also.

Numerous studies have derived warfarin dosing algorithms that use both genetic and nongenetic factors to predict warfarin dose. Two algorithms perform well in estimating stable warfarin dose and were created using more than 5,000 subjects, although as noted above, more recent data suggest they do not perform acceptably in African Americans when used without modification for *CYP2C9* alleles frequently found in the African population. The Gage and International Warfarin Pharmacogenetics Consortium (IWPC) algorithms or minor adjustments to them have also been the algorithms used in both randomized controlled trials and most of the prospective dosing studies. Dosing algorithms using genetic information outperform nongenetic clinical algorithms and fixed-dose approaches in dose prediction, except in African Americans when the algorithm only includes *CYP2C9*\*2 and \*3. Genetics-based algorithms also better predict warfarin dose than the FDA-approved warfarin label table.

## Pharmacogenetic Algorithm-based Warfarin Dosing

This guideline recommends that pharmacogenetic warfarin dosing be accomplished through the use of one of the pharmacogenetic dosing algorithms described above, as summarized in Figure 2 in the original guideline document. These algorithms, as originally published, are available in the Supplement (see the "Availability of Companion Documents" field). The two algorithms provide very similar dose recommendations. The clinical and genetic information used in one or both algorithms is shown in Text Box 1 in the original guideline document. These algorithms compute the anticipated stable daily warfarin dose to one decimal and the clinician must then prescribe a regimen (e.g., an estimate of 4.3 mg/day might be given as 4 mg daily except 5 mg 2 days per week). An additional "dose revision" algorithm, which can be used on days 4–5 of therapy for dose refinement and uses genetic information, was tested in the COAG and EU-PACT trials and can also be used (Supplemental Table S5).

It is important to note that these algorithms do not include *CYP4F2*, *CYP2C9*\*5, \*6, \*8, or \*11 or rs12777823, and incorporation of these should be added when results are available, as described in Figure 2. The [WarfarinDosing.org](http://WarfarinDosing.org)  contains both algorithms, the Gage algorithm as the primary algorithm and the IWPC algorithm as the secondary algorithm and can adjust for *CYP4F2*, *CYP2C9*\*5, and \*6. If utilizing [WarfarinDosing.org](http://WarfarinDosing.org) , the user should be clear on whether the algorithm is or is not incorporating genotypes beyond *CYP2C9* \*2 and \*3 and *VKORC1*, which are the only three genotypes in the original version of both algorithms.

### Pharmacogenetics-informed Loading (or Initiation) Dose Calculation

The use of a different initial warfarin dose (or "loading dose") is somewhat controversial and plays different roles in different regions of the world, based on experience and local standards. Recent data from a diverse U.S.-based cohort suggest that failure to provide a loading dose in patients with zero or one variant alleles in *VKORC1* or *CYP2C9* may delay time to therapeutic INR and reduce time in therapeutic range in the initial month of therapy. A genetically guided loading dose approach was developed by Avery et al. and a slightly modified version was successfully implemented in the EU-PACT trial. In COAG *CYP2C9* variant alleles were not considered for the initial dose, providing a small loading dose on day 1. Whether differences in loading dose strategies between the EU-PACT and COAG trials contributed to differing results is not known. If loading doses are to be used, a genetically informed approach to calculating the loading dose may be helpful. The majority of the experience with a genetically informed loading regimen is in those of European ancestry. Determination of maintenance dose would be as described above.

### Non-African Ancestry Recommendation

In patients who self-identify as non-African ancestry, the recommendation, as summarized in Figure 2, is to: 1) calculate warfarin dosing using a published pharmacogenetic algorithm, including genotype information for *VKORC1*-1639G>A and *CYP2C9*\*2 and \*3. In individuals with genotypes associated with *CYP2C9* poor metabolism (e.g., *CYP2C9* \*2/\*3, \*3/\*3) or both increased sensitivity (*VKORC1*-1639 A/A) and *CYP2C9* poor metabolism, an alternative oral anticoagulant might be considered. The bulk of the literature informing these recommendations is in European and Asian ancestry populations, but consistent data exist for other non-African populations. These recommendations are graded as STRONG. 2) If a loading dose is to be utilized, the EU-PACT loading dose algorithm that incorporates genetic information could be used. This recommendation is OPTIONAL. 3) While *CYP2C9*\*5, \*6, \*8, or \*11 variant alleles are commonly referred to as African-specific alleles, they can occur among individuals who do not identify as, or know of their, African ancestry. If these variant alleles are detected, decrease calculated dose by 15% to 30% per variant allele or consider an alternative agent. Larger dose reductions might be needed in patients homozygous for variant alleles (i.e., 20% to 40%, e.g., *CYP2C9*\*2/\*5). This recommendation is graded as OPTIONAL. 4) If the *CYP4F2*\*3 (i.e., c.1297A, p.433Met) allele is also detected, increase the dose by 5% to 10%. This recommendation is also considered OPTIONAL. 5) The data do not suggest an association between rs12777823 genotype and warfarin dose in non-African Americans, thus rs12777823 should not be considered in these individuals (even if available).

### African Ancestry Recommendation

In patients of African ancestry, *CYP2C9*\*5, \*6, \*8, \*11 are important for warfarin dosing. If these genotypes are not available, warfarin should be dosed clinically without consideration for genotype. If *CYP2C9*\*5, \*6, \*8, and \*11 are known, then the recommendation, as shown in Figure 2, is to: 1) calculate warfarin dose using a validated pharmacogenetic algorithm, including genotype information for *VKORC1* c.-1639G>A and *CYP2C9*\*2 and \*3; 2) if the individual carries a *CYP2C9*\*5, \*6, \*8, or \*11 variant allele(s), decrease calculated dose by 15% to 30%. Larger dose reductions might be needed in patients who carry two variant alleles (e.g., *CYP2C9*\*5/\*6) (i.e., 20% to 40% dose reduction). 3) In addition, rs12777823 is associated with warfarin dosing in African Americans (mainly originating from West Africa). Thus, in African Americans a dose reductions of 10% to 25% in those with rs12777823 A/G or A/A genotype is recommended. These recommendations are considered MODERATE.

In individuals with genotypes that predict *CYP2C9* poor metabolism or who have increased warfarin sensitivity (*VKORC1* c.-1639 A/A) and *CYP2C9* poor metabolism, an alternative oral anticoagulant should be considered, for non-African ancestry. As noted above, if a loading dose is to be used, the EU-PACT algorithm that incorporates genetic information could be used to calculate loading dose. This recommendation is OPTIONAL. The data do not support an impact on clinical phenotype for *CYP4F2* on warfarin dosing in those of African ancestry and so no recommendation is made for use of *CYP4F2* genotype data in blacks.

### Recommendations for Pediatric Patients

As detailed in Supplemental Table S7, there is strong evidence for the use of *CYP2C9*\*2 and \*3 and *VKORC1*-1639G>A genotype to guide warfarin dosing in children of European ancestry. The studies in Japanese pediatric individuals are conflicting, as *VKORC1* and *CYP2C9* could not be adequately evaluated due to the low numbers of *CYP2C9* variant carriers. For other ethnicities, there is no evidence documenting that *VKORC1* and *CYP2C9* are important. Furthermore, there are no data in children that included *CYP2C9*\*5, \*6, \*8, or \*11 genotyping. Based on the current evidence, in children of European ancestry and if *CYP2C9*\*2 and \*3 and *VKORC1*-1639 genotype are available, calculate warfarin dosing based on a validated published pediatric pharmacogenetic algorithm (see Figure 3 in the original guideline document). A dosing tool that can be used in children of European ancestry is available at <http://www.warfarindoserevision.com> .

### Other Considerations

Given the effects of *CYP2C9* on warfarin clearance, and given that the *CYP2C9* variant alleles are associated with reduced warfarin clearance, *CYP2C9* genotype may influence time to onset and offset of anticoagulation, as measured by INR. The Supplemental Material summarizes other considerations in the dosing of warfarin, including clinical factors and interacting drugs, some of which are included in the pharmacogenetic dosing algorithms (see Text Box 1 in the original guideline document). Other genes of potential importance are detailed in the Supplemental Material and Supplemental Table S6, including *CALU* and *GGCX*. Most clinical genotyping platforms do not include these genes, nor do the dosing tables or published algorithms. The Supplemental Material also discusses incorporation of genetic information into the initial dose, and alternatives to warfarin.

### Definitions

#### Strength of Therapeutic Recommendations

**Strong:** The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

**Moderate:** There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

**Optional:** The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

**No recommendation:** There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

# Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Dosing recommendations for warfarin dosing based on genotype for adult patients
- Dosing recommendations for warfarin dosing based on genotype for pediatric patients

Specific dosing algorithms are provided in the supplemental material (see the "Availability of Companion Documents" field).

## Scope

### Disease/Condition(s)

Thromboembolic disorders

### Guideline Category

Management

Prevention

Treatment

### Clinical Specialty

Cardiology

Internal Medicine

Medical Genetics

Pediatrics

Pharmacology

Pulmonary Medicine

### Intended Users

Advanced Practice Nurses

Nurses

Pharmacists

Physician Assistants

Physicians

### Guideline Objective(s)

To assist in the interpretation and use of cytochrome P450 2C9 (*CYP2C9*), vitamin K epoxide reductase complex subunit 1 (*VKORC1*), cytochrome P450 4F2 (*CYP4F2*), and rs12777823 genotypes to estimate therapeutic warfarin dose among patients with a target international normalized ratio (INR) of 2–3,

should clinical genotype results be available to the clinician

## Target Population

Patients requiring management or treatment of thromboembolic disorders

## Interventions and Practices Considered

Use of cytochrome P450 2C9 (*CYP2C9*), vitamin K epoxide reductase complex subunit 1 (*VKORC1*), cytochrome P450 4F2 (*CYP4F2*), and the *CYP2C* cluster (e.g., rs12777823) genotyping to guide use of warfarin

## Major Outcomes Considered

Effect of cytochrome P450 2C9 (*CYP2C9*), vitamin K epoxide reductase complex subunit 1 (*VKORC1*), cytochrome P450 4F2 (*CYP4F2*), and the *CYP2C* cluster (e.g., rs12777823) on warfarin clinical outcomes or effect on pharmacokinetics

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

#### Literature Review

The authors searched the PubMed® database (January 1966 to August 2016) for the following keywords: ((cytochrome P450 2C9 or *CYP2C9*) OR (*VKORC1*) OR (cytochrome P450 4F2 or *CYP4F2*) AND (warfarin) AND English [Language]). Using these search terms, 1221 publications were identified. In addition, studies annotated in PharmGKB (<http://www.pharmgkb.org> ) were identified. Study inclusion criteria included publications that included analyses for the association between *CYP2C9/VKORC1/CYP4F2* genotypes and metabolism of warfarin or warfarin-related adverse drug events or clinical outcomes. Non-English manuscripts were excluded.

The *CYP2C9/VKORC1/CYP4F2* frequency tables (see the "Availability of Companion Documents" field) were made by searching the PubMed® database (1995 to 2016). The following criteria were used for *CYP2C9*: (*CYP2C9* or 2C9 or cytochrome P4502C9) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity OR population) with filter limits set to retrieve "full-text" and "English" literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the *CYP2C9* frequency table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses). Similar search strategies were used for *VKORC1* and *CYP4F2* genes. Allele frequencies reported in phase 3 1000 Genomes were also included (<http://phase3browser.1000genomes.org/index.html> ).

## Number of Source Documents

Following application of the inclusion criteria, 151 publications were reviewed and included in the evidence tables (Supplemental Tables S1- S7 [see the "Availability of Companion Documents" field]).

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

### Levels of Evidence Linking Genotype to Phenotype

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type or variant-containing gene, *in vitro* enzyme activity from tissues isolated from individuals of known genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies. The gene-based dosing recommendations in this guideline take into consideration the effects cytochrome P450 2C9 (*CYP2C9*)/vitamin K epoxide reductase complex subunit 1 (*VKORC1*)/cytochrome P450 4F2 (*CYP4F2*) genetic variants may have on both clinical outcomes and warfarin pharmacokinetics.

### Summarization and Presentation of the Evidence Linking Genotype to Drug Variability

Publications supporting a major finding are usually considered as a group and scored by members of the writing committee based on the totality of the evidence supporting that major finding. Thus, it is possible for an evidentiary conclusion based on many papers, each of which may be relatively weak, to be graded as "moderate" or even "strong," if there are multiple small case reports or studies that are all supportive with no contradictory studies. The rating scheme (see the "Rating Scheme for the Strength of the Evidence" field) uses a scale modified slightly from Valdes et al. Primary publications are summarized in the Evidence Table which is published in the manuscript supplemental material (see the "Availability of Companion Documents" field). It is the writing committee's evaluation of this evidence that provides the basis for the therapeutic recommendation(s).

## Methods Used to Formulate the Recommendations

## Description of Methods Used to Formulate the Recommendations

### Identification of Content Experts and Formation of Writing Committee

Once a guideline topic has been approved by Clinical Pharmacogenetics Implementation Consortium (CPIC) members and the Steering Committee, a senior author is identified through self-nomination or by request of the CPIC Steering Committee. The senior author takes responsibility for forming the writing committee and completing the guideline. The writing committee is multidisciplinary, comprising a variety of scientists, pharmacologists, and clinicians (e.g., pharmacists and physicians). Authors will have a track record of publication and/or expertise in the specific topic area of the guideline. PharmGKB assigns at least one Scientific Curator to each CPIC guideline writing committee who has expertise in searching, compiling and evaluating the evidence for gene-drug associations, and making it computable and available on the PharmGKB Web site. Furthermore, PharmGKB curators often take primary responsibility for completing background gene and drug summaries, assigning likely phenotypes based on genotypes (i.e., "Table 1" in guidelines), literature review, as well as preparing supplementary material provided in each guideline (i.e., genotypes that constitute the star (\*) alleles or haplotypes, frequencies of alleles in major race/ethnic groups, genetic test interpretation and availability, and evidence linking genotype with phenotype).

### Development of Therapeutic Recommendation and Assignment of Strength of the Recommendation

The writing committee discusses the evaluation of the literature and develops a draft recommendation via Web conferences and email communication. CPIC's therapeutic recommendations are based on weighing the evidence summarized in the supplementary Evidence Table from a combination of preclinical functional and clinical data, as well as on any existing consensus guidelines. Evidence related to the suitability of alternative medications or dosing that may be used based on genetics must be weighed in assigning the strength of the recommendation. Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians and are presented in the Table 2 of each guideline and occasionally in an algorithm.

To assign strength to a recommendation, CPIC uses a transparent three category system (see the "Rating Scheme for the Strength of the Recommendations" field) for rating recommendations that was adopted with slight modification from the rating scale for evidence-based recommendations on the use of antiretroviral agents (<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf> ). Each recommendation also includes an assessment of its usefulness in pediatric patients.

CPIC guidelines currently focus on gene-drug pairs for which at least one of the prescribing recommendations is actionable (e.g., recommendation to alter a dose or consider an alternative drug based on the genotype-phenotype relationship). For these and many other gene-drug pairs, PharmGKB also contains clinical annotations that are genotype-based summaries of the association between a drug and a particular variant. Each clinical annotation is assigned a level of evidence depending on population, replication, effect size and statistical significance.

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for additional information.

## Rating Scheme for the Strength of the Recommendations

### Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

## Cost Analysis

The cost-benefit of genetic-guided therapy depends on the cost of genotyping and the reduction in adverse events, and most insurance plans do not currently pay for warfarin pharmacogenetic testing.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

### Internal and External Review, Comment, and Approval Process

Once the writing committee has completed and approved a draft guideline, the draft guideline is circulated to the Clinical Pharmacogenetics Implementation Consortium (CPIC) co-leaders and coordinator for content review. The guideline is reviewed for compliance with the CPIC Standard Operating Procedures and required format. The guideline draft is then discussed on a CPIC conference call with all CPIC members and circulated to the members for further review and approval. At each stage, feedback is considered for incorporation into the guideline and/or revision of the guideline, as supported by the available evidence and expert clinical judgment of the senior author and writing committee. Finally, the guideline manuscript undergoes typical external scientific peer review by the journal prior to publication. Current agreements with the American Society for *Clinical Pharmacology and Therapeutics* give the journal *Clinical Pharmacology and Therapeutics* the first right of refusal for publication of CPIC guidelines; as part of this agreement, the guidelines are freely posted to PharmGKB immediately upon publication. In general *Clinical Pharmacology and Therapeutics* uses a minimum of two external expert peer-reviewers and an editorial board member with content expertise as reviewers for each CPIC guideline.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The evidence summarized in Supplemental Tables S1 to S7 (see the "Availability of Companion Documents" field) is graded on a scale of high, moderate, and weak, based upon the level of evidence (see the Rating Scheme for the Strength of the Evidence" field). Every effort was made to present evidence from high-quality studies.

## Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Incorporation of genetic information has the potential to shorten the time to stable international normalized ratio (INR), increase the time within the therapeutic INR range, and reduce underdosing or overdosing during the initial treatment period. If these benefits are achieved, they could result in a reduced risk of bleeding and thromboembolic events.

## Potential Harms

Using genetic information to guide dosing may lead to false security and inadequate international normalized ratio (INR) monitoring. In particular, there are risks of using pharmacogenetic dosing in those of African ancestry if only cytochrome P450 2C9 (*CYP2C9*) \*2 and \*3 alleles are included. Genetic-guided dosing may increase the risk for overdosing or underdosing, especially in individuals who carry rare or untested variants and are assigned as "wild-type" by default. Although there is substantial evidence associating *CYP2C9* and vitamin K epoxide reductase complex subunit 1 (*VKORC1*) variants with warfarin dosing, randomized clinical trials have demonstrated inconsistent results in terms of clinical outcomes (see "Linking genetic variability to variability in drug-related phenotypes" in the original guideline document). Although genotyping is reliable when performed in qualified laboratories, an additional risk is an error in genotyping or reporting of genotype. Genotypes are life-long test results, so such error could have long-term adverse health implications.

## Qualifying Statements

### Qualifying Statements

#### Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

Many pharmacogenetic dosing algorithms are developed for a target international normalized ratio (INR) of 2–3 and so their utility for estimating therapeutic warfarin doses with other target INR ranges is uncertain; however, some algorithms accommodate the target INR explicitly. Pharmacogenetic-guided warfarin dosing does not alter the requirements for regular INR monitoring. There are patients for whom genetic testing is likely to be of little or no benefit, including those who already have had long-term treatment with stable warfarin doses and those who are unable to achieve stable dosing due to variable adherence. The greatest potential benefit is early in the course of therapy (before therapy initiation or in the early days of therapy). It is likely that patients on therapy for many weeks to months, with careful INR monitoring, will derive little benefit from subsequent warfarin pharmacogenetics testing.

#### Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision-making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to persons or property arising out of or related to any use of CPIC's guidelines, or for any errors or omissions.

#### Underlying Assumption

The key underlying assumption for all CPIC guidelines is that clinical high-throughput and pre-emptive

genotyping will eventually become common practice and clinicians will increasingly have patients' genotypes available before a prescription is written. Therefore, CPIC guidelines are designed to provide guidance to clinicians as to how available genetic test results should be interpreted to ultimately improve drug therapy, rather than to provide guidance as to whether a genetic test should or should not be ordered.

## Implementation of the Guideline

### Description of Implementation Strategy

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for information on guideline dissemination and connecting the guidelines to practice.

### Implementation Tools

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Staying Healthy

### IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

Johnson JA, Caudle KE, Gong L, Whirl-Carrillo M, Stein CM, Scott SA, Lee MT, Gage BF, Kimmel SE, Perera MA, Anderson JL, Pirmohamed M, Klein TE, Limdi NA, Cavallari LH, Wadelius M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. Clin Pharmacol Ther. 2017 Sep;102(3):397-404. [46 references] [PubMed](#)

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2017 Sep

## Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

## Source(s) of Funding

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## Guideline Committee

The Writing Committee

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

### Conflicts of Interest

J.A.J. is on the Clinical Pharmacogenetics Implementation Consortium (CPIC) Steering Committee and has no conflicts of interest related to this guideline. T.E.K and M.W.C. are paid scientific advisors to the Rxight Pharmacogenetic Program. S.A.S. is a director of a clinical laboratory that performs *CYP2C9* and *VKORC1* genetic testing. All other authors declare no conflicts of interest related to this guideline.

### Management of Conflicts of Interest

All authors must declare any funding interests and activities potentially resulting in conflict of interest by written disclosure to the CPIC Steering Committee and writing committee before the approval of the authorship plan. Included are all possible conflicts including spouses/family members in declarations, National Institutes of Health (NIH) funding that could be interpreted to indicate that authors are "advocates" of the recommendations, as well as any sources of revenue from consulting, patents, stock ownership, etc. All conflicts of interest are reported in the guideline manuscript.

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the [Clinical Pharmacogenetics Implementation Consortium \(CPIC\) Web site](#)

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## Availability of Companion Documents

The following are available:

Supplementary material, including tables and methodological information, is available from the [Clinical Pharmacogenetics Implementation Consortium \(CPIC\) Web site](#) .

A variety of resources, including allele definition, frequency, and functionality tables, drug resource mappings, and gene resource mapping are available from the [CPIC Web site](#) .

Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr Drug Metab.* 2014;15(2):209-17. Available from the [National Center for Biotechnology Information \(NCBI\) Web site](#) .

## Patient Resources

None available

## NGC Status

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